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Tannins and Related Compounds. XL.[1] Revision of the Structures of Punicalin and Punicalagin, and Isolation and Characterization of 2-*O*-Galloylpunicalin from the Bark of *Punica granatum* L.

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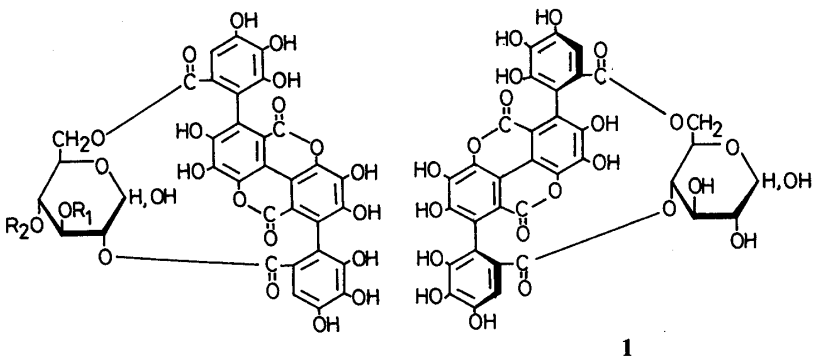
The structures of punicalin and punicalagin, isolated from the bark of *Punica granatum* L. (pomegranate), have been revised to 4,6-(*S*,*S*)-gallagyl-D-glucose (**1**) and 2,3-(*S*)-hexahydroxydiphenoyl-4,6-(*S*,*S*)-gallagyl-D-glucose (**2**), respectively, on the basis of chemical and spectroscopic evidence. In addition, a new hydrolyzable tannin, 2-*O*-galloyl-4,6-(*S*,*S*)-gallagyl-D-glucose (**3**) was isolated from the same plant source, and characterized.

Keywords——*Punica granatum*; pomegranate; Punicaceae; punicalin; punicalagin; 2-*O*-galloylpunicalin; gallagylglucose; hydrolyzable tannin

In the course of systematic chemical examinations on vegetable tannins, Mayer and his co-workers isolated yellow-colored hydrolyzable tannins, punicalin and punicalagin, from the pericarp of *Punica granatum* L. (pomegranate) (Punicaceae), and proposed the novel structures (**1′** and **2′**) for these tannins.[2] Subsequently, our examination[3] of the same plant revealed that the pattern of the composition of tannins differs remarkably in different parts of the plant, particularly between the leaf and pericarp, and that punicalin and punicalagin are almost entirely absent in the leaf, although these tannins predominate in the pericarp. These findings prompted us to investigate the tannin components of the bark, which has been used since ancient times as a taeniacide, and is regarded as a rich source of tannins; this work resulted in the isolation of a new hydrolyzable tannin (**3**), together with considerable amounts of punicalin and punicalagin. During the structural elucidation of the tannin (**3**), some doubt



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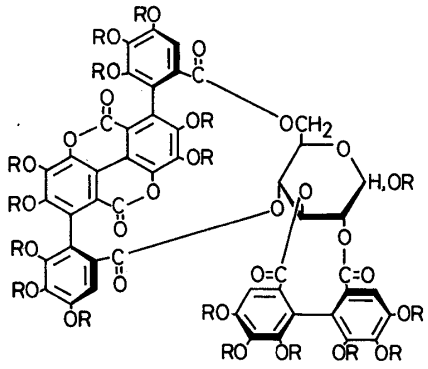
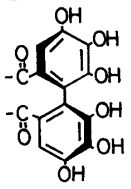


2: R=H
9: R=Me

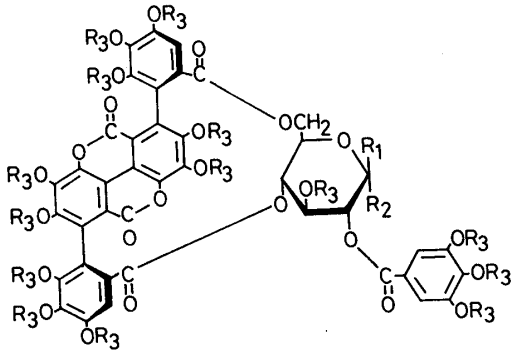
1′: $R_1=R_2=H$

2′: $R_1, R_2=$

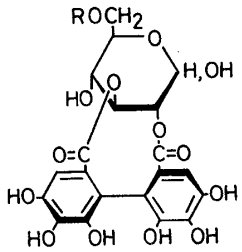


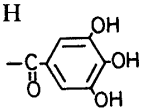
arose as to the location of the tetraphenyl (gallagyl) ester group on the glucopyranose ring in punicalin and punicalagin, and re-examination has led to the revision of their structures to **1** and **2**, respectively. We now wish to give a detailed account of the structural determination of punicalin and punicalagin, and also of the isolation and characterization of the new hydrolyzable tannin (**3**).

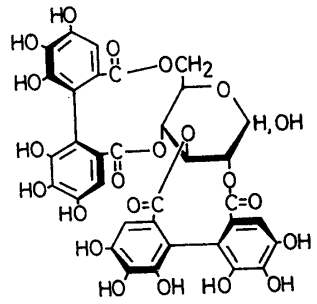
The chromatographic techniques used in previous studies[4] were applied to the separation of individual tannin constituents occurring in the aqueous acetone extract of the bark to yield the tannins (**1**, **2** and **3**), together with 2,3-(*S*)-hexahydroxydiphenoyl-D-glucose (**4**),[5] 6-*O*-galloyl-2,3-(*S*)-hexahydroxydiphenoyl-D-glucose (**5**)[6] and 2,3;4,6-bis-(*S*)-hexahydroxydiphenoyl-D-glucose (pedunculagin) (**6**).[5] The identity of the tannins (**1** and **2**) with punicalin and punicalagin obtained by Mayer *et al.* was confirmed by direct comparisons.[7]



3: R_1, R_2=H, OH; R_3=H
7: R_1=H, R_2=OAc, R_3=Ac



4: R=H
5: R= 



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The structurally unknown tannin (**3**) was obtained as a yellow crystalline powder (H_2O), mp 255° (dec.), $[\alpha]_D$ +3.8° (MeOH), $C_{41}H_{26}O_{26}\cdot H_2O$. A characteristic yellow color in aqueous solution and the appearance of two high-field carboxyl signals (δ 158.5 and 159.8) in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum were consistent with the presence of a gallagyl group in the molecule. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed a two-proton singlet at δ 6.94, suggesting the presence of a galloyl group. On enzymatic hydrolysis with tannase, **3** yielded gallic acid and a yellow hydrolysate which was identified as punicalin by comparison of their ^{1}H-NMR spectral data.

In the high-resolution (500 MHz) ^{1}H-NMR spectrum, the absence of an acyl group at the anomeric center was confirmed by the observation of duplicated signals due to glucopyranose ring protons, although the α-anomer was highly predominant (Fig. 1). The coupling pattern and the chemical shifts of the sugar proton signals were related to those found in punicalin, apart from a remarkable low-field shift (δ+1.5) of a double-doublet signal assignable to the C_2-proton, indicating that the additional galloyl group was attached to the C_2-position. This conclusion, however, conflicted with the structures (**1′** and **2′**) of punicalin and punicalagin proposed by Mayer and his collaborators.

The evidence for the locations of the acyl groups, obtained by Mayer *et al.*, was based mainly on the coloring test and the examination of a Dreiding model.[2] Namely, punicalin was negative to the aniline–hydrogen–phthalate reagent despite the lack of an acyl group at the anomeric center. They considered this characteristic to be consistent with that found in 2-*O*-galloylglucose,[8] although most hydrolyzable tannins such as 2,3-(*S*)-hexahydroxydiphenoyl-D-glucose (**4**) are positive to this test. In addition, their inspection of a Dreiding model that the large distance between the two carboxyl groups in the gallagyl residue limited the positions of the two acyl groups to C_2 and C_6.

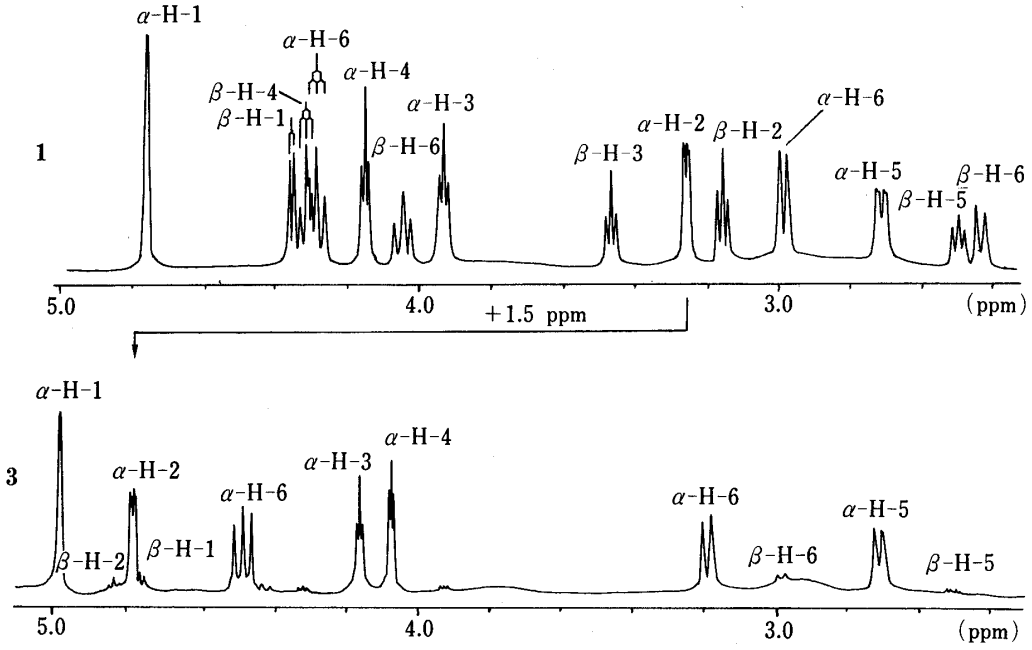

Fig. 1. 500 MHz ^{1}H-NMR Spectra of Punicalin (**1**) and Compound **3** (in Acetone-d_6)

In the ^{13}C- and ^{1}H-NMR spectra of punicalin, the low-field shifts [δ 63.5 and 4.05 (β), 4.29 (α)] of the glucose C_6 and the C_6-methylene signals [compared with those (δ 62.1 and 3.28) of 1-*O*-galloylglucose] indicated that one of the carboxyl groups was indeed located at this position, and the gallagyl group was therefore considered to be attached to either the C_3, C_6- or the C_4, C_6-positions. To clarify this point, the ^{1}H-NMR chemical shifts of glucose signals in compound **3** were compared with those of the pentadecaacetate (**7**) prepared by acetylation of **3**. As is clear from Fig. 2, the C_1- and C_3-H signals in the acetate (**7**) were shifted downfield by δ 0.8 and 1.5, respectively, while the chemical shifts of the signals due to C_2-, C_4- and C_6-H were almost unchanged. Taking account of the presence of a galloyl group at the C_2-position, these observations indicated that the gallagyl group should be located at the C_4, C_6-positions. Thus, compound **3** was characterized as 2-*O*-galloyl-4,6-gallagyl-D-glucose (**3**), and punicalin as 4,6-gallagyl-D-glucose (**1**). Furthermore, since punicalagin afforded punicalin and ellagic acid on partial acid hydrolysis, the structure of punicalagin could be assigned as 2,3-hexahydroxydiphenoyl-4,6-gallagyl-D-glucose (**2**).[9]

Dimethyl decamethylgallagiate (**8**), which was obtained by alkaline methanolysis of the punicalagin heptadecamethyl ether (**9**), possessed optical activity, $[\alpha]_D$ $-73.7°$, owing to the presence of two asymmetric centers. Of the four possible atrop-isomers (*S*,*S*; *R*,*R*; *S*,*R*; *R*,*S*), the observation of the optical activity thus excluded the two meso-forms (*S*,*R*; *R*,*S*). In order to determine the atrop-isomerism of the gallagyl group, the following synthetic examination was carried out. Drastic methylation of the ester (**8**) with dimethyl sulfate in a strongly alkaline medium, and subsequent treatment with diazomethane afforded two isomers (**10** and **11**). On the other hand, intermolecular coupling reaction of the optically active 3-bromo compound (**12**),[5] prepared by partial bromination of dimethyl-(*S*)-hexamethoxydiphenoate (**13**)[10] provided two diastereoisomers, which were shown to be identical with **10** and **11** by thin-layer chromatography (TLC) and infrared (IR) spectral comparisons. Although the optical activities of the synthetic samples were somewhat diminished by partial racemization, comparison of the circular dichroism (CD) spectra of the synthetic samples with those obtained from punicalagin showed identical signs of the Cotton effects (Fig. 3). Thus, the chirality of the gallagyl group was concluded to be in the *S*-series.

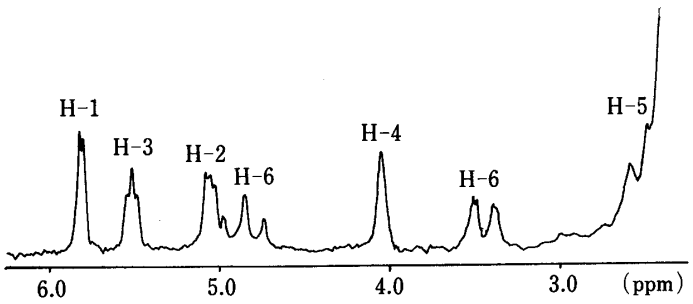

Fig. 2. 100 MHz ^{1}H-NMR Spectrum of the Pentadacaacetate (7) (in $CDCl_3$)

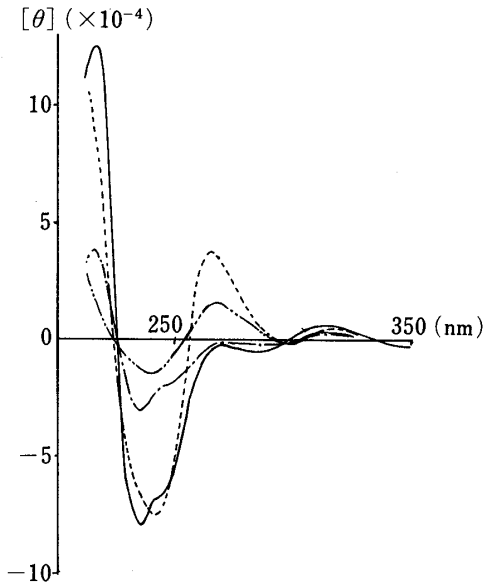

Fig. 3. CD Spectra of the Methyl Ethers

——, **10** (from punicalagin); ------, **11** (from punicalagin); – – – –, **10** (synthesized); – – – – –, **11** (synthesized).

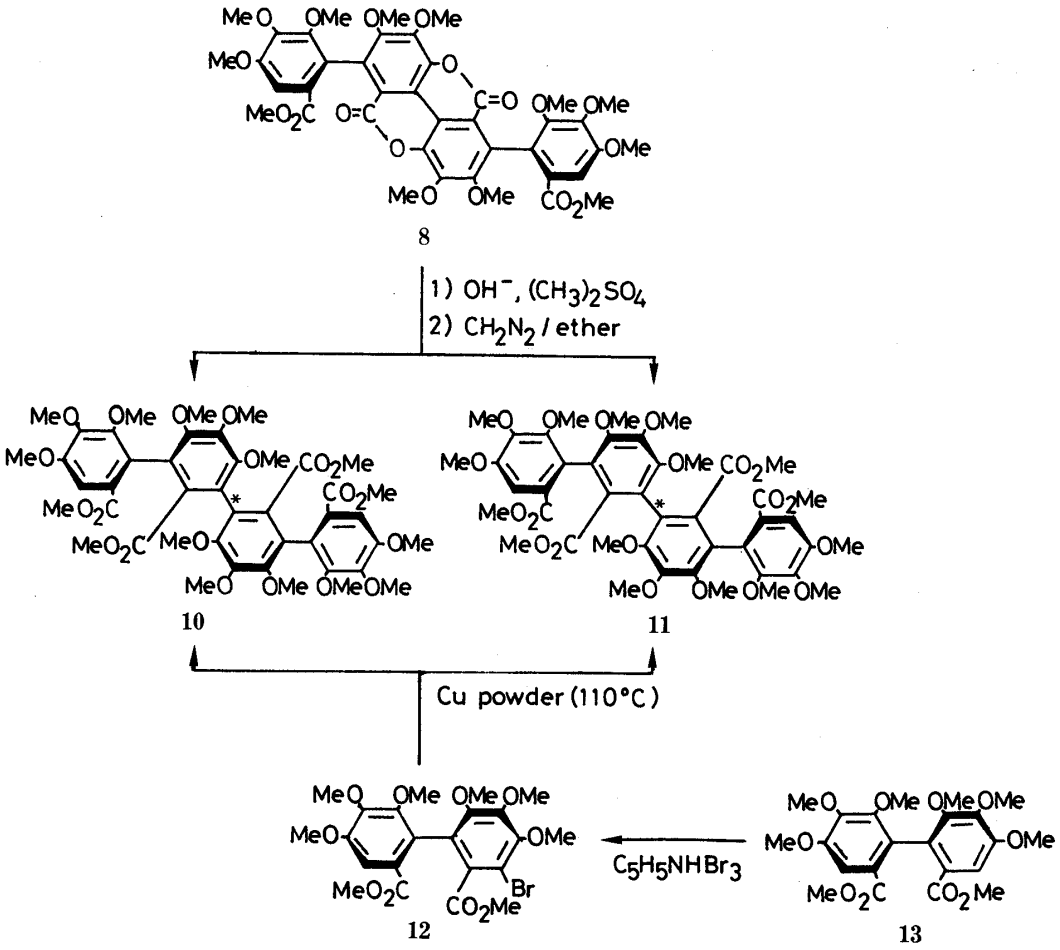

Chart 1

Compounds **10** and **11** are epimers at this bond.

On the basis of the evidence described above, punicalin, punicalagin and the new tannin were characterized as 4,6-(*S*,*S*)-gallagyl-D-glucose (**1**), 2,3-(*S*)[10]-hexahydroxydiphenoyl-4,6-(*S*,*S*)-gallagyl-D-glucose (**2**) and 2-*O*-galloyl-4,6-(*S*,*S*)-gallagyl-D-glucose (**3**), respectively.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter (cell length: 0.5 dm). IR spectra were recorded with a JASCO IR-G spectrometer, and field-desorption (FD-) and electron impact (EI-) mass spectra (MS) with JEOL D-300 and JEOL DX-300 spectrometers. ^{1}H (100 MHz)- and ^{13}C (25.05 MHz)-NMR spectra were taken with JEOL PS-100 and JEOL FX-100 spectrometers, respectively, and ^{1}H (500 MHz)-NMR spectra with a JEOL FX-500 spectrometer, with tetramethylsilane as an internal standard; chemical shifts are given on a δ (ppm) scale. CD data were obtained in methanol with a JASCO J-20 spectropolarimeter. Column chromatography was carried out with Sephadex LH-20 (25—100 μ, Pharmacia Fine Chemical Co., Ltd.), MCI-gel CHP-20P (75—150 μ, Mitsubishi Chemical Industries Ltd.) and Kieselgel 60 (70—230 mesh, Merck). TLC was performed on precoated Kieselgel 60 F_{254} plates (0.20 mm, Merck) with (A) benzene–ethyl formate–formic acid (1 : 5 : 2) and (B) benzene–acetone (4 : 1), and on precoated cellulose F_{254} plates (0.10 mm, Merck) with (C) 2% acetic acid and (D) the upper layer of butan-1-ol–acetic acid–H_2O (4 : 1 : 5), and the spots were detected by their fluorescence under ultraviolet (UV) light, and with a ferric chloride reagent spray.

Isolation of Tannins 1—6——The fresh bark (5 kg) of *Punica granatum* L. was chopped into small pieces, and extracted at room temperature with 90% aqueous acetone. After removal of the acetone by evaporation under reduced pressure (*ca.* 40 °C), the aqueous solution was subjected to Sephadex LH-20 column chromatography using H_2O with increasing amounts of EtOH to give six fractions; frs. I (80 g), II (40 g), III (44 g), IV (66 g), V (171 g), and VI (81 g). Fraction I deposited a crystalline mass on standing at room temperature, and repeated recrystallization from 60% aqueous MeOH yielded mannitol as colorless needles (*ca.* 30 g). Fraction II was treated with MeOH, and the insoluble materials were filtered off. After concentration, the filtrate was applied to a column of MCI-gel CHP-20P using H_2O with an increasing amount of MeOH (0—20%) to afford 2,3-(*S*)-hexahydroxydiphenoyl-D-glucose (**4**) (2.7 g). Chromatography of fr. III over Sephadex LH-20 with EtOH gave two further fractions; Frs. III-a (15 g) and III-b (5.5 g). Rechromatography of fr. III-a on Sephadex LH-20 with H_2O–MeOH (3 : 2, v/v) afforded punicalin (**1**) (4.4 g). Fraction IV was further divided by MCI-gel CHP-20P chromatography using H_2O–MeOH (1 : 9—2 : 3, v/v) into three fractions; frs. IV-a (3.9 g), IV-b (14.5 g), and IV-c (18.2 g). Crystallization of fr. IV-b from H_2O afforded compound **3** (5.6 g). Sephadex LH-20 chromatography of fr. V with EtOH afforded two further fractions; frs. V-a (36 g) and V-b (130 g). Fraction V-a was chromatographed over Sephadex LH-20 and then MCI-gel CHP-20P using H_2O with increasing amounts of MeOH to yield 6-*O*-galloyl-2,3-(*S*)-hexahydroxydiphenoyl-D-glucose (**5**) (240 mg). Chromatography of a part (10 g) of fr. V-b on Sephadex LH-20 using a variety of solvent systems, *viz.* 60% aqueous MeOH, MeOH, and EtOH–H_2O–acetone (27 : 18 : 5, v/v), gave pedunculagin (**6**) (412 mg) and punicalagin (**2**) (6.9 g).

Punicalin (1)——A yellow amorphous powder, $[\alpha]_D^{28}$ −81.1 ° (c = 0.6, H_2O). *Anal.* Calcd for $C_{34}H_{22}O_{22}\cdot H_2O$: C, 51.01; H, 3.02. Found: C, 50.93; H, 3.05. ^{1}H-NMR (acetone-d_6): 6.68 (3/7H, s), 6.77 (4/7H, s), 7.06 (3/7H, s), 7.17 (4/7H, s), Fig. 1. ^{13}C-NMR (acetone-d_6): 63.5, 65.5, 69.9, 71.9, 72.9, 74.1, 75.3, 89.1 (α-C_1), 97.1 (β-C_1), 158.4, 158.5, 159.5 (δ-lactone), 168.1, 169.0, 169.7 (CO_2). The ^{1}H-NMR spectrum was identical with that of an authentic sample which was prepared from punicalagin by partial acid hydrolysis.

Punicalagin (2)——A yellow amorphous powder, $[\alpha]_D^{28}$ −162.2 ° (c = 1.30, H_2O). *Anal.* Calcd for $C_{43}H_{28}O_{30}\cdot H_2O$: C, 52.28; H, 2.74. Found: C, 52.22; H, 2.86. ^{1}H-NMR (acetone-d_6): 2.16 (m, H-5), 3.16—3.36 (m, H-6), 4.06—4.30 (m, H-6), 6.53, 6.61, 6.68, 7.02 (each s, aromatic H). ^{13}C-NMR (acetone-d_6): 64.3, 66.8, 71.1, 71.6, 72.6, 74.5, 76.5, 78.9, 90.2 (α-C_1), 94.4 (β-C_1), 157.9, 158.4 (δ-lactone), 168.1, 168.4, 168.8, 169.3, 169.5 (CO_2). These spectral data were identical with those of an authentic sample.[7]

Compound 3——A yellow crystalline powder (H_2O), mp 255 °C (dec.), $[\alpha]_D^{28}$ +3.8 ° (c = 0.9, MeOH). *Anal.* Calcd for $C_{41}H_{26}O_{26}\cdot H_2O$: C, 51.69; H, 2.96. Found: C, 51.71; H, 2.95. ^{1}H-NMR (acetone-d_6): 6.34 (s), 6.50 (s), 6.94 (s, galloyl-H), 7.00 (s, galloyl-H) 7.21 (s), 7.25 (s), Fig. 1. ^{13}C-NMR (acetone-d_6): 62.9 (C_6), 66.7, 70.9, 71.7, 73.8, 86.4 (α-C_1), 110.4 (galloyl-$C_{2,6}$), 120.3 (galloyl-C_1), 158.5, 159.8 (δ-lactone), 166.1, 168.0, 169.1 (CO_2).

Enzymatic Hydrolysis of 3 with Tannase——Tannase dissolved in H_2O was added dropwise to a solution of **3** (200 mg) in H_2O (20 ml), and the mixture was incubated at 37 °C for 3 h. Evaporation of the solvent afforded a residue, which was treated with EtOH. The EtOH-soluble portion was applied to a column of Sephadex LH-20 with EtOH to give gallic acid (36 mg) and punicalin (**1**) (147 mg).

Acetylation of 3——**3** (100 mg) was acetylated with acetic anhydride and pyridine at room temperature. Usual work-up yielded the pentadecaacetate (**7**) (32 mg), a white powder (MeOH), mp 217—219 °C, $[\alpha]_D^{24}$ −3.4 ° (c = 0.3, $CHCl_3$). *Anal.* Calcd for $C_{71}H_{56}O_{41}\cdot H_2O$: C, 53.86; H, 3.69. Found: C, 53.99; H, 3.49. ^{1}H-NMR ($CDCl_3$): 1.98—2.40 (m, Ac), 7.47 (1H, s, aromatic H), 7.53 (2H, s, galloyl-H), 7.98 (1H, s, aromatic H), Fig. 2.

Partial Acid Hydrolysis of 2——A solution of **2** (300 mg) in 1 N sulfuric acid (5 ml) was heated (90 °C) for 7 h. The

resulting pale yellow needles (60 mg) was collected by filtration and recrystallized from pyridine. This compound was identified as ellagic acid by comparison of the IR spectrum with that of an authentic sample. The filtrate was neutralized with aqueous $NaHCO_3$ solution and then directly subjected to Sephadex LH-20 chromatography using H_2O with increasing amounts of MeOH to give punicalin (**1**) (113 mg).

Methylation of 2——A mixture of **2** (500 mg), anhydrous potassium carbonate (1.7 g) and dimethyl sulfate (1.5 ml) in dry acetone (20 ml) was refluxed for 5 h with stirring. After removal of inorganic salts by filtration, the filtrate was concentrated to a syrup, which was chromatographed over silica gel. Elution with benzene–acetone (9 : 1, v/v) gave the heptadecamethyl ether (**9**) (41 mg), a pale yellow powder (MeOH), mp 225—228 °C, $[\alpha]_D^{24}$ −143.6° (c = 0.6, $CHCl_3$). *Anal.* Calcd for $C_{65}H_{62}O_{30} \cdot H_2O$: C, 58.21; H, 4.81. Found: C, 58.15; H, 4.89. FD-MS m/z: 1322 (M^+). ^{1}H-NMR ($CDCl_3$): 6.68, 6.70, 6.77, 7.42 (each 1H, s, aromatic H).

Methanolysis of 9——A 3% methanolic solution of NaOMe was added dropwise to a solution of the heptamethyl ether (**9**) in MeOH (15 ml), and the mixture was stirred at room temperature for 69 h. After neutralization with Amberlite IR-120B (H^+ form) resin, the solution was concentrated to a syrup, which was chromatographed over silica gel. Elution with benzene–acetone (19 : 1, v/v) gave dimethyl (*S*)-hexamethoxydiphenoate (**13**) (14 mg), a colorless syrup, $[\alpha]_D^{28}$ −25.4° (c = 1.6, $CHCl_3$), and dimethyl (*S,S*)-decamethylgallagiate (**8**) (11 mg), yellow prisms (MeOH), mp 276—278 °C. $[\alpha]_D^{28}$ −73.7° (c = 0.2, $CHCl_3$). *Anal.* Calcd for $C_{40}H_{38}O_{18}$: C, 59.55; H, 4.75. Found: C, 59.48; H, 5.05. EI-MS m/z: 806 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1720 (CO_2). ^{1}H-NMR ($CDCl_3$): 3.66 (12H, s, OCH_3), 3.70, 3.97, 3.99, 4.20 (each 6H, s, OCH_3), 7.50 (2H, s, aromatic H). CD (c = 3.0×10^{-5}, CH_3CN) $[\theta]^{26}$ (nm): -14.1×10^4 (245) (negative maximum), $+2.58 \times 10^4$ (264) (positive maximum), -2.70×10^4 (276) (negative maximum), $+1.25 \times 10^4$ (322) (positive maximum). These spectral data are consistent with those reported by Mayer *et al.*[2]

Further Methylation of 8——A solution of dimethyl (*S,S*)-decamethylgallagiate (**8**) (10 mg) in a mixture of MeOH (2 ml) and 10% aqueous NaOH (1 ml) was heated (90 °C) for 1 h. Then dimethyl sulphate (0.3 ml) and 10% aqueous NaOH (0.5 ml) were added, and the mixture was further heated for 1 h. After cooling, the solution was acidified with HCl, and extracted with ether. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give a residue, which was treated with ethereal CH_2N_2 for 1 h. After removal of the solvent by evaporation, the residue was chromatographed over silica gel (benzene–acetone, 47 : 3, v/v) to afford the methyl ether (**10**) (4 mg), a colorless syrup, $[\alpha]_D^{25}$ +3.2° (c = 0.4, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2925, 1720, 1520. EI-MS m/z: 898 (M^+), CD (c = 1.1×10^{-4}, MeOH): Fig. 3, and the methyl ether (**11**) (1.3 mg), a colorless syrup, $[\alpha]_D^{25}$ −31.2° (c = 0.2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2920, 1720, 1520. CD (c = 1.4×10^{-4}, MeOH): Fig. 3.

Preparation of 10 and 11——A mixture of (*S*)-dimethyl 3-bromo-4,4′,5,5′,6,6′-hexamethoxydiphanoate (**12**) (120 mg), prepared in the same manner as described in the previous paper,[5] and copper powder (500 mg) was heated at 110 °C for 11 h under a nitrogen atmosphere. After cooling, the reaction mixture was treated with ether (15 ml), and the ether-soluble portion was concentrated to yield a yellow syrup, which was chromatographed over silica gel. Elution with benzene–acetone (47 : 3, v/v) afforded the methyl ether (**10**) (1 mg), a colorless syrup, $[\alpha]_D^{25}$ 0° (c = 0.1, $CHCl_3$). CD (c = 1.1×10^{-4}, MeOH): Fig. 3. Further elution with the same solvent afforded the methyl ether (**11**) (1 mg), $[\alpha]_D^{25}$ −17.1° (c = 0.1, $CDCl_3$). CD (c = 7.2×10^{-5}, MeOH): Fig. 3.

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10) Optically active dimethyl hexamethoxydiphenoate (**13**) was obtained by alkaline methanolysis of the punicalagin heptadecamethyl ether (**9**), and its absolute configuration was confirmed as *S* on the basis of the $[\alpha]_D$ measurement, $[\alpha]_D$ −25.4° ($CHCl_3$).